

**Hepatic Events in oral
antidiabetic – exposed patients
in a Midwestern employer
claims database
(preliminary data)**

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March 26, 1999**

PRELIMINARY DATA: NOT FOR QUOTATION

Midwestern Employer Database Study

- Population of 1.6 million persons in midwestern employer insurance database (1994-1998)
- 14,379 persons exposed to oral antidiabetics
- 10,713 persons with exposed from 1/1/95 through 9/30/98 with at least 6 months eligibility prior to first Rx and eligible for all benefits during period:
 - **New Diabetics (ND): no prior oral antidiabetics**
 - **Established Diabetics(ED): prior oral antidiabetic therapy**

PRELIMINARY DATA: NOT FOR QUOTATION

Midwest Employer Database

Methods

- All patients were followed from first Rx for each antidiabetic to end of eligibility period
- Counted if prior Rx in last 60 days
- Cohorts examined by drug exposure, thus not mutually exclusive
- Thus New Diabetic for Drug 1 would be Established
- Diabetic for next antidiabetic Rx
- All health care utilization, hepatic events and liver function monitoring identified for each patient by both calendar and therapy month

PRELIMINARY DATA: NOT FOR QUOTATION

Midwest Employer Database

Study Population

[Each cohort not mutually exclusive]

10,713 Diabetics on Oral Therapy 1995-98

| Glyburide | Glipizide | Metformin | Troglitazone | Acarbose |
|---------------------|----------------------|----------------------|---------------------|--------------------|
| 522 EDs 2130 NDs | 1136 EDs 2153 NDs | 4393 EDs 1363 NDs | 2471 EDs 217 NDs | 612 EDs 109 NDs |

Overall demographics:

~ 42 % Female; 58% Males for each

Age < 20: < 1%

20-39 2.4-3.7%

40-59 68-74%

60-64 21-29%

[Age > 65 not reliably covered for Rx]

PRELIMINARY DATA: NOT FOR QUOTATION

ICD-9CM CODES

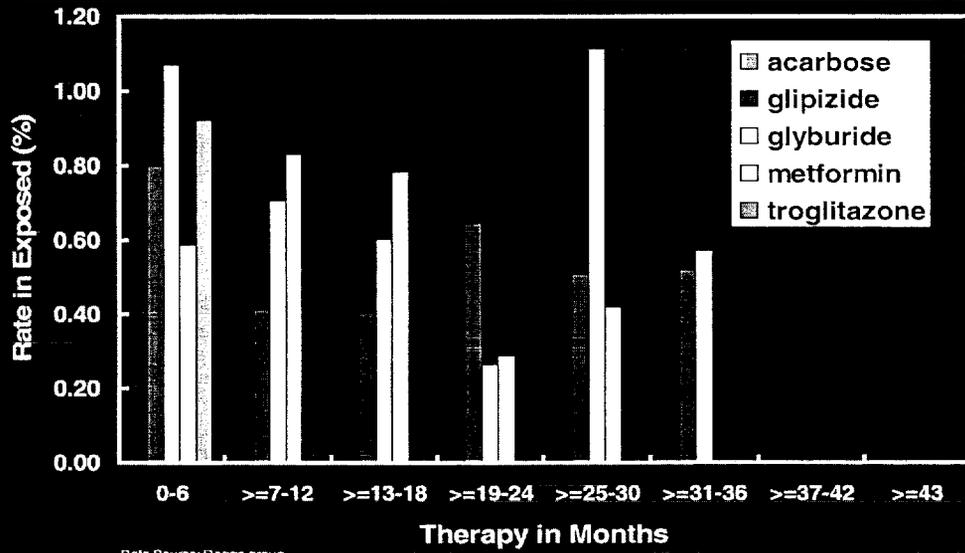
- 570 -Acute and subacute Necrosis of Liver
- 572.2- Hepatic Coma
- 573.3- Hepatitis, Unspecified
- 573.9- Liver Disorder, Unspecified
- 782.4- Jaundice
- E932.3- Adverse Effects In Diabetic Due to Diabetic Medication

Source: International Classification of Diseases(ICD-9-CM) 1998 Edition

PRELIMINARY DATA: NOT FOR QUOTATION

Summary of Hepatic Events Rate by Therapy Duration

New Patients Only

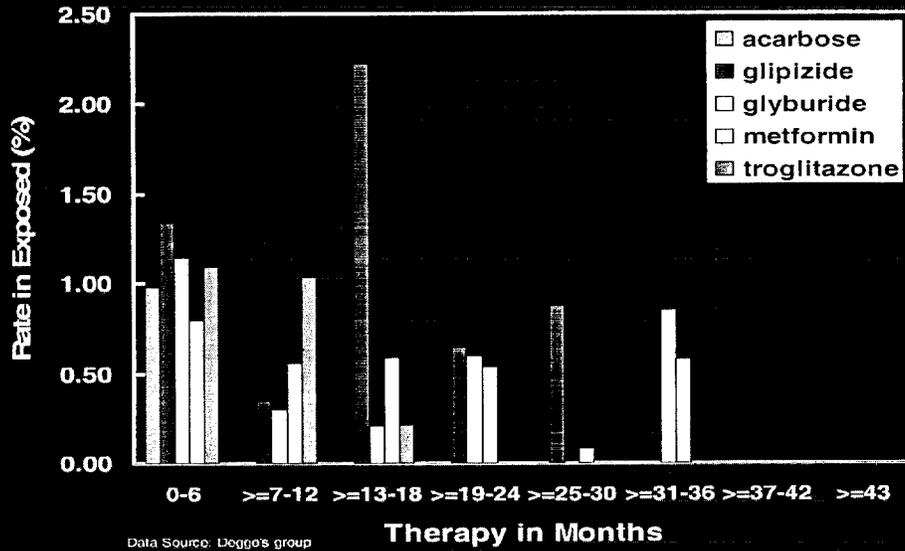


Data Source: Degge group

PRELIMINARY DATA: NOT FOR QUOTATION

Summary of Hepatic Events Rate by Therapy Duration

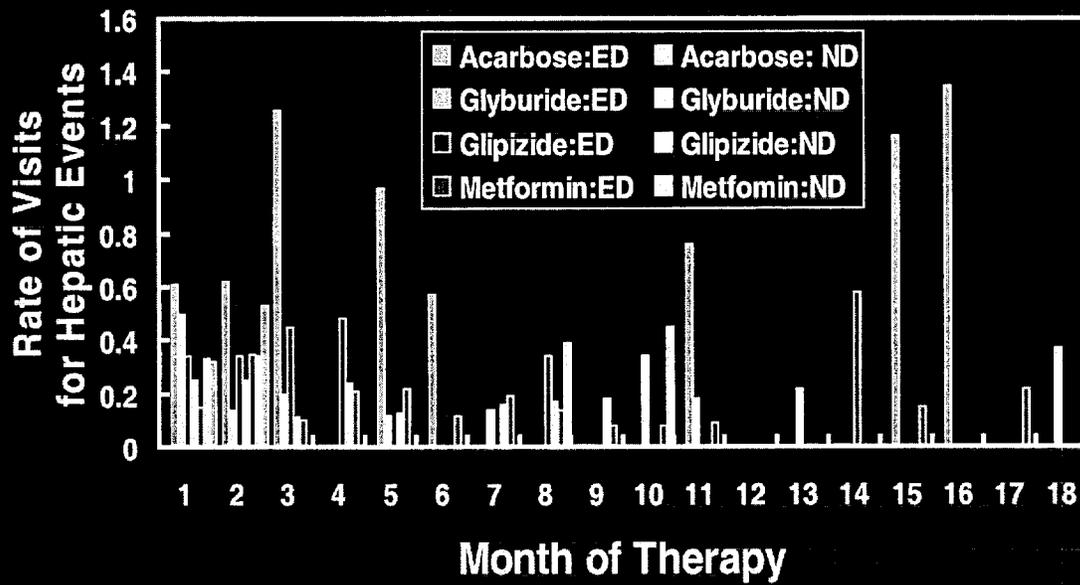
Established Patients Only



Data Source: Degge's group

PRELIMINARY DATA: NOT FOR QUOTATION

Rates of Hepatic Events in Patients on Oral Antidiabetics Prior to 1997



PRELIMINARY DATA: NOT FOR QUOTATION

Cases of Hepatic Necrosis, Coma or Jaundice

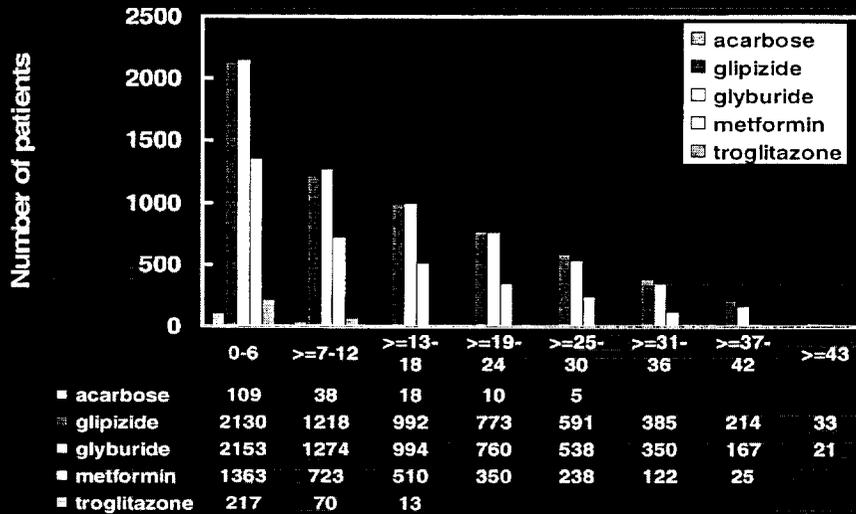
Oral Antidiabetic-Exposed Patients
Midwestern Database

| Exposure Group | N | ICD 9 Code Group | | | |
|----------------|------|------------------|----------|------|----------|
| | | Transplant | Necrosis | Coma | Jaundice |
| Glyburide | 2652 | 1 | - | - | 4 |
| Glipizide | 3289 | - | 3 | 1 | 2 |
| Metformin | 5756 | - | 1 | 1 | 5 |
| Troglitazone | 2688 | - | - | - | 1* |
| Acarbose | 721 | - | - | - | 1 |

*2 Other cases occurred before troglitazone available.

PRELIMINARY DATA: NOT FOR QUOTATION

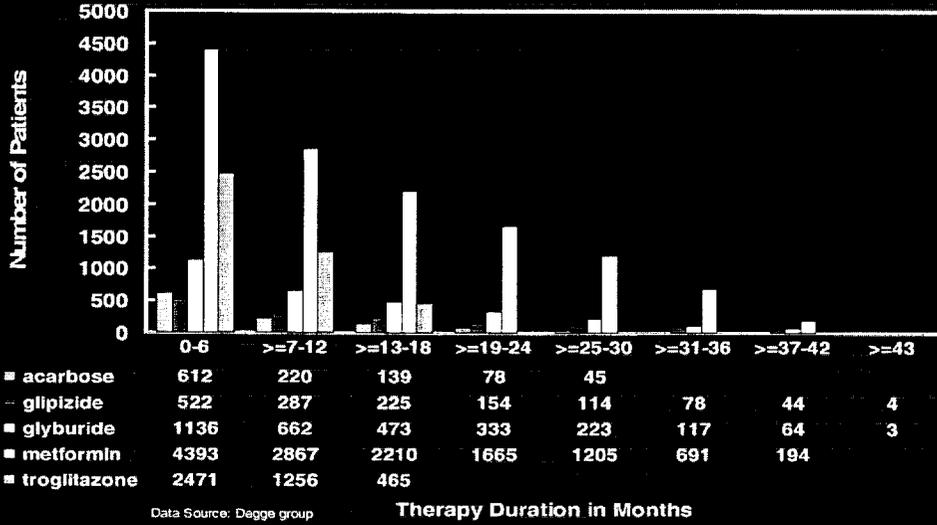
Summary of Number of Patients Exposed by Therapy Duration New Patients Only



Data Source: Degge group Therapy Duration in Months

PRELIMINARY DATA: NOT FOR QUOTATION

Summary of Number of Patients Exposed by Therapy Duration Established Patients Only



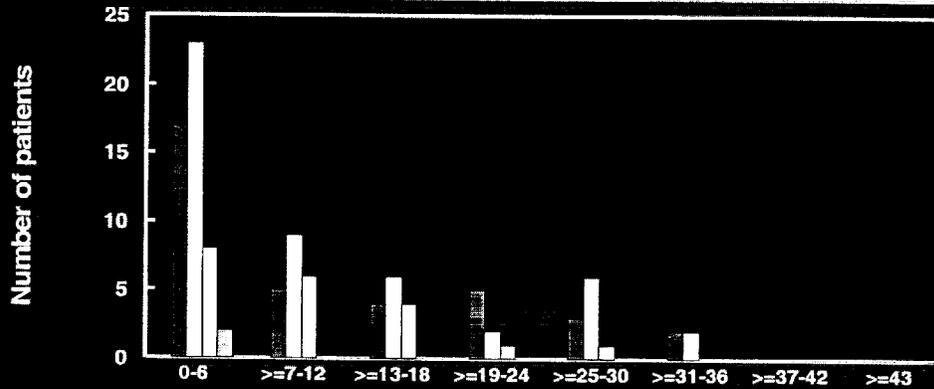
Data Source: Degge group

Therapy Duration in Months

PRELIMINARY DATA: NOT FOR QUOTATION

Summary of Hepatic Events by Therapy Duration

New Patients Only



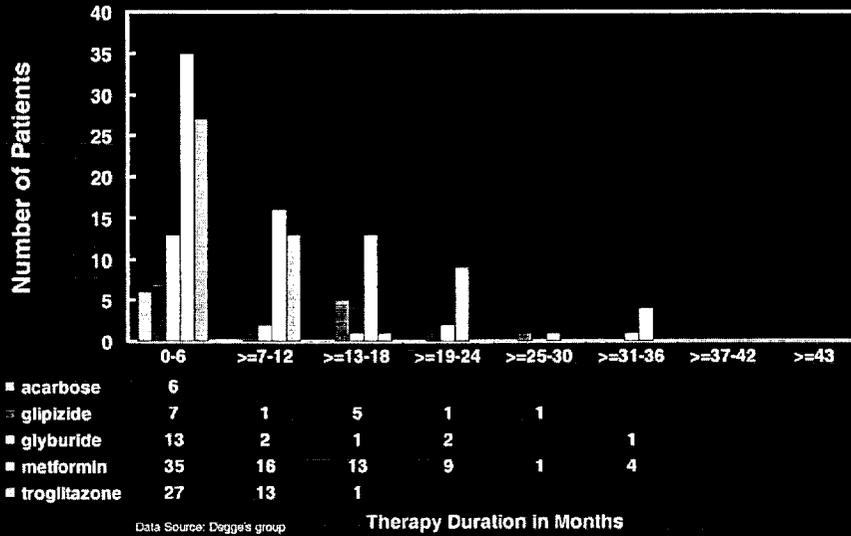
| | 0-6 | >=7-12 | >=13-18 | >=19-24 | >=25-30 | >=31-36 | >=37-42 | >=43 |
|----------------|-----|--------|---------|---------|---------|---------|---------|------|
| ■ acarbose | 17 | 5 | 4 | 5 | 3 | 2 | | |
| ■ glipizide | 23 | 9 | 6 | 2 | 6 | 2 | | |
| ■ metformin | 8 | 6 | 4 | 1 | 1 | | | |
| ■ troglitazone | 2 | | | | | | | |

Data Source: Degge group

Therapy Duration in Months

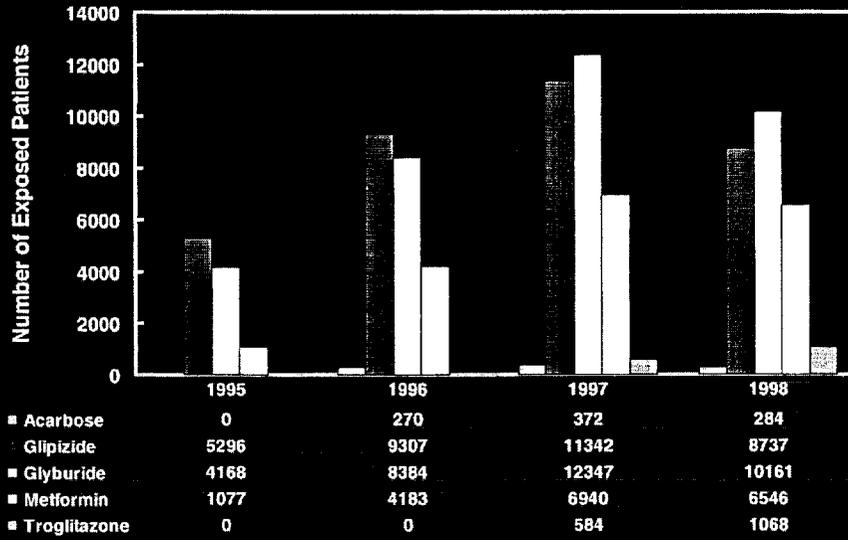
PRELIMINARY DATA: NOT FOR QUOTATION

Summary of Hepatic Events by Therapy Duration Established Patients Only



PRELIMINARY DATA: NOT FOR QUOTATION

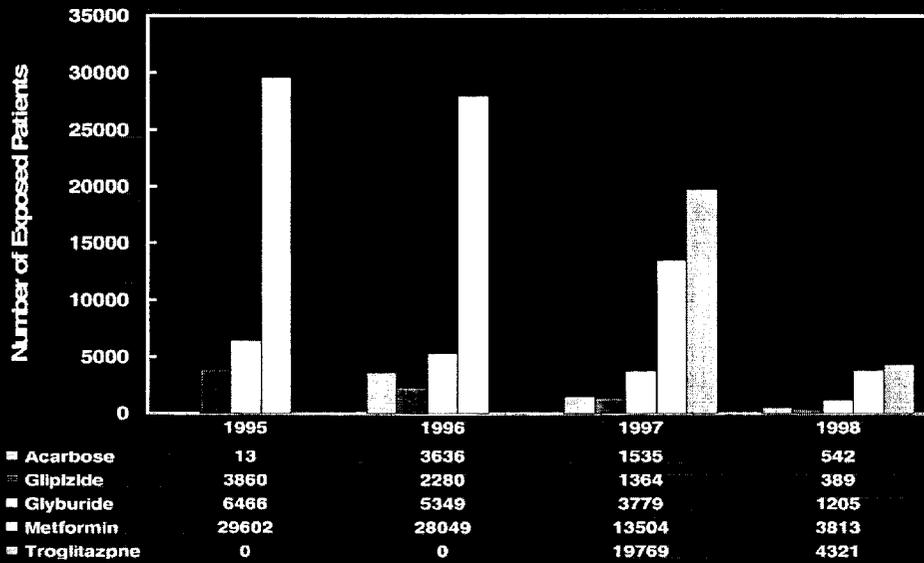
Summary of Hepatic Data of Total Patient Exposure by Calendar Year New Patients Only



PRELIMINARY DATA: NOT FOR QUOTATION

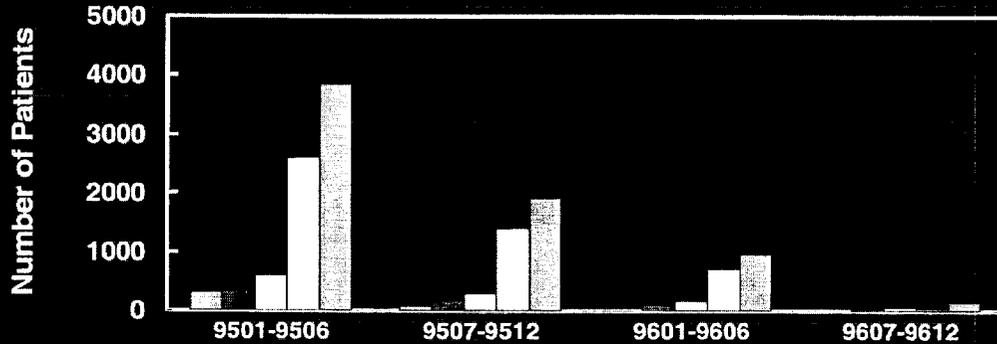
Summary of Hepatic Data by First Therapy Start Year

Established Patients Only



PRELIMINARY DATA: NOT FOR QUOTATION

Summary of Number of Patients Exposed by Therapy Duration Established Patients Only



| | 9501-9506 | 9507-9512 | 9601-9606 | 9607-9612 |
|---------------|-----------|-----------|-----------|-----------|
| ■ acarbose | 315 | 67 | | |
| ■ glipizide | 327 | 158 | 91 | 39 |
| ■ glyburide | 593 | 292 | 163 | 63 |
| ■ metformin | 2605 | 1392 | 700 | 44 |
| ■ Grand Total | 3840 | 1909 | 954 | 146 |

Data Source: Degge group

Therapy Duration in Months

PRELIMINARY DATA: NOT FOR QUOTATION

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Addendum to March 26, 1999 Briefing Book

Please note the following revisions to the March 26, 1999 Briefing Book:

| <u>Page</u> | <u>Revision</u> |
|-------------|---|
| 11 | Last full paragraph: As per Dr. Watkins' update, total liver-related death, regardless of causality, is 75. |
| 17 | Change in incidence table: Line 1 – 1 in 45,000 Line 3, right column – 1 in 103,545 |
| 22 | Carryover paragraph: No Rezulin-treated patients were identified in telephone survey. |